Remarks

Claims 1-16 are pending. By this Amendment, Applicants have amended claim 10. No new matter is introduced. Accordingly, claims 1-16 are currently pending.

Specification

One page 2 of the August 27, 2007 Office Action, the Examiner objected to the term "sustantially" on page 10, line 4, and required the term be corrected to "substantially".

In response, Applicants point out that the term "substantially" occurs at line 24, and not at line 4, on page 10 of the subject specification. Applicants have amended the specification in accordance with the Examiner's request.

Rejection Under 35 U.S.C. §112 - Claim 10

On page 2 and 3 of the August 27, 2007 Office Action, the Examiner rejected claim 10 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner also asserted that the term "substantially" typographically recited as "substantially" is vague and indefinite because it is not clear just how much or how less time period would qualify as "substantially concurrent".

In response, to advance the prosecution but without conceding correctness of the foregoing rejection, Applicants have amended claim 10 to not recite "substantially". Accordingly, the rejection of claim 10 is moot.

Rejection Under 35 U.S.C. §103 – Claims 1-12

On pages 3-5 of the August 27, 2007 Office Action, the Examiner alleged that claims 1-12 are unpatentable over Youdim et al. (WO 95/11016) of record in view of Orru et al. (1999) and further in view of Kaal et al. of record.

Specifically, the Examiner alleged that Youdim et al. teach Applicant's active agent, R(+)-N-propargyl-1-aminoindan (Rasagiline) useful for the treatment of a subject afflicted with Parkinson's disease and a neurodegenerative disease. The Examiner further alleged that Youdim et al. teach the therapeutically effective amount of the agent is about 0.1 mg to about 100 mg (page 23, lines 27-32, claim 29). The Examiner asserted that these amounts encompass Applicant's amounts set forth in claims 4 and 12, and that Youdim et al. teach that pharmaceutically acceptable salts of the agent include, but are not limited to, the mesylate, maleate, fumarate, tartrate, acetate, phosphate and sulfate salts (page 21, line 34, through page 22, line 4). The Examiner further asserted that Youdim et al. teaches that Rasagiline is a selective irreversible inhibitor of the B-form of monoamine oxidase enzyme (page 1, lines 15-29). The Examiner indicated that Youdim et al. do not teach the treatment of amyotrophic lateral sclerosis (ALS) and further comprising 2-amino-6-trifluoromethoxy benzothiazole (riluzole) and its amounts.

On page 4 of the August 27, 2007 Office Action, the Examiner alleged that Orru et al. teach that MAO-B hyperactivity account of the dopaminergic deficiency demonstrated in ALS like in Parkinson's disease (PD); and that Orru et al. teach that the formation of neurotoxic metabolites arising from the oxidative deamination catalyzed by MAO-B may be one of the causes for ALS

as it is suggested in PD. (page 595 right-hand column lines 30-33)

On page 4 of the August 27, 2007 Office Action, the Examiner alleged that Kaal et al. teach that riluzole is a drug currently used for the treatment of amyotrophic lateral sclerosis, and that ALS is a neurodegenerative disease characterized by selective motor neuron death.

The Examiner asserted that it would have been obvious to one of ordinary skill in the art to employ Rasagiline for the treatment of ALS because Youdim et al. teach that Rasagiline is useful for the treatment of a neurodegenerative disease and Parkinson's disease by inhibition of MAO-B enzyme and because MAO-B enzyme hyperactivity exhibits dopaminergic deficiency in ALS as taught by Orru et al. The Examiner alleged that there is a reasonable expectation of successfully treating a dopaminergic deficiency in ALS in patients by administration of Rasagiline because Orru et al. teach that hyperactivity of MAO-B enzyme exhibits dopaminergic deficiency in ALS and because Rasagiline is an irreversible MAO-B inhibitor that reduces MAO-B enzyme production as taught by Youdim et al.

The Examiner further alleged that it would have been obvious to one of ordinary skill in the art to combine riluzole in its therapeutic amounts with Rasagiline for the treatment of ALS because each of the active agents, particularly riluzole is a drug currently used for the treatment of neurodegenerative disease such as ALS, and because Rasagiline is useful for treating symptoms of dopaminergic deficiency in ALS, one would have been motivated to combine Riluzole and Rasagiline in a single formulation for the treatment of ALS in order to achieve an expected additive effect of treating a patient suffering from

ALS. The Examiner concluded that the claims fail to patentably distinguish over that state of the art as represented by the cited references.

Applicants Response:

In response, Applicants submit that the use of rasagiline (claims 1-4) for the treatment of ALS is neither taught nor suggested by the prior art, nor does the prior art provide any expectation that rasagiline would treat ALS.

Furthermore, Applicants submit that the use of rasagiline and riluzole together (claims 5-12) for the treatment of ALS is neither taught nor suggested by the prior art, nor does the prior art provide any expectation that the use of rasagiline and riluzole together would treat ALS.

Introduction

Applicants claim a method of using rasagiline to treat ALS, and a method of using rasagiline with riluzole to treat ALS. Thus, in the former method, Applicants seek to patent a new use for rasagiline, and in the latter method Applicants seek to patent combination therapy involving rasagiline and riluzole. The new use and the combination therapy are both unobvious in view of the prior art, each for independent reasons as discussed below.

M.P.E.P. 2112.02 states that, "the discovery of a new use for an old structure based on unknown properties of the structure might be patentable to the discoverer as a process of using." *Loctite Corp.* v. *Ultraseal Ltd.*, 781 F.2d 861, 875, 228 USPQ 90, 99 (Fed. Cir. 1985) determined that "Even if a composition is old, a process using a known composition in a new and unobvious way may be patentable." Combination therapy is also patentable if the

combination is unobvious.

In order to establish a *prima facie* case of obviousness, it must be shown through explicit analysis that the claimed invention is no more than the "predictable use" of the prior art. *KSR v. Teleflex*, 550 U.S. _____ (2007). Applicants respectfully submit that the effects of rasagiline on ALS, and of the combination treatment on ALS, could not be predicted from the prior art.

I) One of skill in the art would not reasonably expect to be able to successfully treat ALS with Rasagiline

Prior to Applicants' invention, rasagiline had been neither taught nor suggested as a treatment for ALS. Certainly, nothing in the prior art provided any expectation that rasagiline would be an effective treatment for ALS, the effects of rasagiline on ALS could not be predicted from the prior art.

Contrary to the Examiner's position, it is unreasonable to expect every MAO-B inhibitor to successfully treat ALS. There is evidence in the prior art that ALS cannot be treated by a MAO-B inhibitor, which like Rasagiline is also a Parkinson's disease treatment. Selegiline is an irreversible MAO-B inhibitor used to treat Parkinson's disease. However, Selegiline was found to be ineffective in ALS (Lange et al. (1998) "Selegiline Is Ineffective in a Collaborative Double-blind, Placebo-Controlled Trial for Treatment of Amyotrophic Lateral Sclerosis" Arch. Neurol. 55: 93-96), copy attached as **Exhibit 1**.

Therefore, it is unreasonable and improper for the August 27, 2007 Office Action to assert that one of skill in the art would have a "reasonable expectation of successfully treating a dopaminergic deficiency in ALS in patients by administration of

Rasagiline because Orru et al. teach that hyperactivity of MAO-B enzyme exhibits dopaminergic deficiency in ALS and because Rasagiline is an irreversible MAO-B inhibitor that reduces MAO-B enzyme production as taught by Youdim et al.". There is no evidence in the August 27, 2007 Office Action to support such a statement; in fact, there is clinical evidence to the contrary.

The failed attempt to treat ALS with Selegiline would instill one of skill in the art with the expectation that irreversible MAO-B inhibitors are ineffective to treat ALS. Thus, the failed prior attempt with Selegiline is a clear teaching away from Applicants' claimed invention. Therefore, given the teaching of Lange et al. one of skill in the art would not expect Rasagiline, or Rasagiline in combination with riluzole to effectively treat ALS. It is well settled that "when the prior art teaches away" from the claimed invention, the claimed invention is not obvious. See, e.g. *KSR v. Teleflex*, 550 U.S. _____ (2007), citing *U.S. v. Adams*, 383 U.S. 39, 40 (1966).

In conclusion, there is nothing in the prior art to suggest that ALS could be treated by Rasagiline. Accordingly, the rejection under 35 U.S.C. §103 is improper and should be withdrawn.

II) The Combination of Rasagiline and Riluzole for the Treatment of ALS also Would not Have Reasonably Been Expected to be Successful by One of Skill in the Art Based on the Prior Art.

In addition to the uncertainties discussed above, one of skill in the art would recognize that combining Rasagiline with riluzole would add yet another layer of uncertainty.

Applicants direct the Examiner to page 4, line 22 through page 5, line 27 of the subject specification for a discussion of the

uncertainties individuals of skill in the art, i.e. the U.S. Food and Drug Administration, recognized with combination therapy. Essentially, one of skill in the art would find the interactions between two drugs when administered together to treat a disease to be wholly unpredictable. Specifically:

> The *in vivo* interactions between two drugs, such as those of the subject invention, are complex. The effects of a drug are related to its absorption, distribution, and elimination. When two drugs are introduced into the body, each drug can affect the absorption, distribution, and elimination of the other and hence, alter the effects of the other. For instance, one drug may inhibit, activate or induce the production of enzymes involved in a metabolic route of elimination of the other drug ("Guidance for Industry"). Thus, when two drugs are administered to treat the same disease, it is unclear whether each will complement the therapeutic activity of the other, have no effect, or interfere with the therapeutic activity of the other.
>
> Not only may the interaction between two drugs affect the intended therapeutic activity of each drug, but the interaction may increase the levels of toxic metabolites ("Guidance for Industry"). The interaction may also heighten or lessen the side effects of each drug.
>
> Additionally, it is difficult to predict when the effects of the interaction between the two drugs will become manifest. For example, metabolic interactions between drugs may become apparent upon the initial

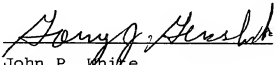
> administration of the second drug, after the two have reached a steady-state of concentration or even upon discontinuation of one of the drugs ("Guidance for Industry").
>
> Thus, the success of one drug or each drug separately in an *in vitro* model, an animal model or even in humans may not translate into success of the administration of both drugs in humans.

Therefore, the prior art would not have motivated one of skill in the art to combine riluzole with rasagiline to treat ALS. Moreover, one of skill in the art would have readily understood the uncertainties associated with combination therapy. Accordingly it is improper to reject applicants' pending claims under 35 U.S.C. §103 and such rejection should be withdrawn.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' undersigned attorneys invite the Examiner to telephone at the number provided below.

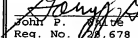
No fee is deemed necessary in connection with the filing of this Amendment. However, if any other fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



John P. White
Registration No. 28,678
Gary J. Gershik
Registration No. 39,992
Attorneys for Applicant
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450



Date

John P. White
Reg. No. 28,678
Gary J. Gershik
Reg. No. 39,992

EXHIBIT 1
Applicants: Eran Blaugrund et al.
Application Serial No.: 10/712,958
Filed: November 13, 2003

ORIGINAL CONTRIBUTION

Selegiline Is Ineffective in a Collaborative Double-blind, Placebo-Controlled Trial for Treatment of Amyotrophic Lateral Sclerosis

Dale J. Lange, MD; Peregrine L. Murphy, MS, MDiv; Beverly Diamond, PhD; Vicki Appel, RN; Eugene C. Lai, MD, PhD; David S. Younger, MD; Stanley H. Appel, MD

Background: The cause of amyotrophic lateral sclerosis (ALS) is not known, and there is no effective treatment. Cell death may be caused by oxidative damage. Selegiline hydrochloride (Eldepryl) is a monoamine oxidase-B inhibitor with antioxidant properties.

Objective: To determine if selegiline affects the clinical course of patients with ALS.

Design: Six-month, double-blind, placebo-controlled study of 133 patients with classical ALS and symptoms for less than 3 years. The primary end point to indicate effectiveness was the rate of change of the Appel ALS total score, an index of disease severity that incorporates strength and function in limbs, respiratory function, and bulbar function.

Results: Of the 133 patients, 67 were randomized to receive selegiline and 66 to receive placebo. One hundred four patients (53 in the selegiline group and 51 in the placebo group) completed the 6-month trial. Both groups were comparable for baseline characteristics and mean Appel ALS total score (70.5 points for the selegiline group and 70.6 for the placebo group). There was no difference in the rate of progression as measured by the Appel ALS total score, showing an average increase of 22 points in 6 months. The monthly rate of change was 3.4 for the selegiline group and 3.5 for the placebo group. There was 1 adverse reaction: worsening depression. Seven patients died during the study (4 in the selegiline group and 3 in the placebo group).

Conclusion: Selegiline treatment had no significant effect on the rate of clinical progression or outcome of ALS.

Arch Neurol. 1998;55:93-96

AMYOTROPHIC lateral sclerosis (ALS) is a progressive neuromuscular disease manifested as weakness and wasting of all skeletal muscles of the body, ending in death due to respiratory failure.[1] The cause is unknown, but possibilities include oxidative damage,[2,3] toxic effects of glutamate,[4] deficiency of neurotrophic factors,[5] chronic viral infection,[6] and immunological attack against motor neurons.[7] Another neurodegenerative disease, Parkinson disease, seems to progress slower when patients are treated with the monoamine oxidase-B (MAO-B) inhibitor selegiline hydrochloride (Eldepryl).[8] To determine if similar effects could be seen in ALS, we performed a randomized, double-blind, placebo-controlled trial.

From the Departments of Neurology, The Neurological Institute, Columbia-Presbyterian Medical Center, New York, NY (Drs Lange, Diamond, and Younger and Ms Murphy); and Baylor College of Medicine (Houston, Tex) (Ms Appel and Drs Lai and Appel).

RESULTS

Of the 133 patients enrolled in the study, 67 were randomized to the selegiline group and 66 to the placebo group. One hundred four patients, 53 in the selegiline group and 51 in the placebo group, completed the 6-month assessment. The patients in both groups were comparable at baseline with respect to age, sex, race, clinical characteristics, and laboratory values (**Table 1**). The mean (±SD) age was 56.9±1.0 years. Slightly more men (n=46 [68.6%]) were randomized to the selegiline group compared with the placebo group (n=36 [54.5%]). No significant differences were found between groups at baseline on the AALS total or component scores (**Table 2**). The mean (±SD) AALS total score at entry was 35.1±1.3 for the selegiline group and 34.9±1.4 for the placebo group.

This article is also available on our Web site: www.ama-assn.org/neuro.

PATIENTS AND METHODS

The study was performed at The Neurological Institute, Columbia-Presbyterian Medical Center, New York, NY, and Baylor College of Medicine, Houston, Tex. One hundred thirty-three patients were randomized after meeting criteria for classical ALS (weakness, wasting, and fasciculations in ≥2 levels of the central nervous system, with pathological reflexes or overactive reflexes in weak, wasted limbs).[9] Patients were excluded if there was evidence of any of the following conditions: multifocal neuropathy with conduction block, paraproteinemia, elevated serum levels of GM1 antibodies, sensorimotor peripheral neuropathy, previous infection with poliovirus, lower motor neuron disease only, primary lateral sclerosis, previous allergy to selegiline, or abnormal results of endocrinologic studies. Patients with serious medical problems or poor family support were deemed to have possible sources of interference with completion of the study, and they were also excluded. The research team at each site consisted of 2 investigators and a study coordinator unaware of randomization status and another investigator who reviewed laboratory data. Informed consent was obtained from each patient after the nature of the study was explained.

Entry criteria included ages from 25 to 65 years, symptom duration of less than 3 years, mild to moderate disease with an Appel ALS (AALS) total score from 30 to 80,[10] and no immunosuppressant therapy or other drug therapy for at least 3 months before enrollment.

The oral selegiline hydrochloride dose was 5 mg twice daily. Patients were randomized to the selegiline or placebo group. Patients were examined at baseline and at 4, 8, 16, and 24 weeks using the AALS score. According to this assessment, a normal person has a total AALS score of 30 points, and a person with a maximal muscle dysfunction has a score of 164 points. People with mild disease who function independently average 52 points; those who can no longer work average 90 points; and patients who are completely bedbound average 135 points.[10] Patients with scores above 115 points or who had forced vital capacities below 39% of predicted values were considered to have treatment failure and entered an open-label phase. All patients admitted to the trial had an AALS total score of less than 65.

Descriptive statistics were computed for selected demographic and clinical characteristics. To assess differences between the treated and untreated groups on these measures, χ^2 and unpaired, 2-tailed t tests were computed. The natural logarithms were used in all t test calculations.

Using an intent-to-treat model, 2 separate analyses were computed to assess the effects of treatment on the progression of the disease. First, the Friedman analysis of variance (ANOVA) using a rate of change was calculated. A rate of change for each patient randomized in the study was calculated using a regression slope. A rate of change was calculated for the overall AALS score and each of its subscales in this manner.

Second, Kaplan-Meier survival curves, using an overall change of 22 points on the overall AALS score as the end point, were calculated. This end point was selected because it represents a major change in a patient's lifestyle and a shift in clinical categories as previously identified.[10] Also, it has been used in other trials.[11] The power of the study was 80% at a level of .05 (n=180).

RATE OF CHANGE

The mean (±SD) rate of change for the AALS total score was 3.4±0.4 for the selegiline group and 3.5±0.5 for the placebo group. Using the rate of change as the dependent measure, a Friedman ANOVA found no significant difference between groups (**Figure 1**). The same analysis was conducted for each of the component AALS scores, ie, bulbar, respiratory, manual muscle, lower extremity function, and upper extremity function. No statistically significant differences were found between groups for any of these analyses (**Table 3**).

We conducted an analysis excluding those patients with a rapid rate of change (ie, a change of ≥48 points during the study) and another including only patients with prominent lower motor neuron involvement (ie, relatively low bulbar and respiratory scores compared with manual muscle score). Other analyses using age at first symptom as a covariate and comparing men and women were considered. The comparisons for all of these models were based on the Friedman ANOVA using rates of change as the dependent measure. No statistically significant difference was found for any of the models.

SURVIVAL ANALYSIS

For this analysis, the end point was calculated based on disease progression. An increase in AALS total score of 22 points was selected based on the clinical implications of a change of this magnitude and because it has been used in other studies.[11] A patient was censored when a progression of 22 points was first seen. As a result, patients could be censored at any evaluation point if they met this requirement. Using this end point, no significant difference was found between groups (Wilcoxon χ^2=0.01; P=.98) (**Figure 2**). At the end of the 6-month study, an equal number of patients from both groups had experienced an increase of 22 points or more in their AALS total score. At month 4, slightly more patients in the placebo group (n=13 [20%]) than in the selegiline group (n=9 [13%]) experienced the increase. This difference was lost in month 6, when the failure rate for both groups was equal. The same analysis was conducted using a progression to 11 points on the AALS total score. Again, the difference was not significant.

ADVERSE REACTIONS

One patient required dose adjustment downward and eventual withdrawal because of worsening depression. No clinically significant hepatotoxic effects were found.

TREATMENT FAILURES AND DEATH

Of the 29 patients not completing the 24-week study, 12 withdrew voluntarily (6 from each group); 9 withdrew

Table 1. Selected Patient Characteristics

	All Patients	Selegiline Hydrochloride Group	Placebo Group
Mean (±SE) age, y			
At first symptom	55.8±1.0	56.7±1.4	54.8±1.4
At first visit	56.9±1.0	57.9±1.4	55.8±1.4
Sex, No. (%) of patients			
Male	82 (61.6)	16 (68.6)	36 (54.5)
Female	51 (38.3)	21 (31.3)	30 (45.4)
First symptom, No. (%) of patients			
Bulbar	29 (21.8)	14 (20.9)	15 (22.7)
Upper extremity	41 (30.8)	20 (29.8)	21 (31.8)
Lower extremity	34 (25.6)	20 (29.8)	14 (21.2)
Bulbar and extremity	6 (4.5)	3 (4.5)	3 (4.5)
Other	23 (17.3)	10 (14.9)	13 (19.7)

Table 2. Mean AALS Total Score and Its Components at Baseline by Treatment Group*

AALS Component Score	Selegiline Hydrochloride Group (n=67)	Placebo Group (n=65)
Total	55.1±1.3	54.9±1.4
Bulbar	8.2±0.1	8.4±0.4
Respiratory	64.1±4.9	59.1±4.8
Manual muscle	9.3±0.6	10.1±0.6
Lower extremity function	13.6±0.6	13.4±0.6
Upper extremity function	12.2±0.7	11.5±0.5

*AALS indicates Appel amyotrophic lateral sclerosis. Data are given as mean±SE.

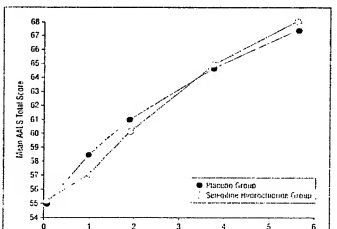


Figure 1. *Mean Appel amyotrophic lateral sclerosis (AALS) score and month of follow-up by treatment group. Groups are described in the "Patients and Methods" section.*

because they reached early termination criteria (AALS total score, >115, or forced vital capacity, <30% of that predicted) (5 in the selegiline group and 4 in the placebo group); and 7 died during the study (4 in the selegiline group and 3 in the placebo group). One patient withdrew because of adverse reactions.

Table 3. Rate of Change for AALS Total Score and Its Components by Treatment Group*

AALS Component Score	Selegiline Hydrochloride Group	Placebo Group
Total	3.4±0.4	3.5±0.5
Bulbar	0.6±0.1	0.8±0.2
Respiratory	−1.6±0.0	−2.2±0.4
Manual muscle	0.8±0.1	0.7±0.1
Lower extremity function	0.6±0.1	0.5±0.1
Upper extremity function	0.7±0.1	0.9±0.2

*AALS indicates Appel amyotrophic lateral sclerosis. Data are given as mean±SE.

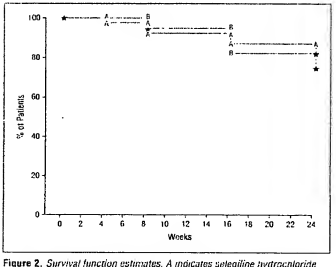


Figure 2. *Survival function estimates. A indicates selegiline hydrochloride group; B, placebo group; and asterisk, intersection of the 2 groups. Groups are described in the "Patients and Methods" section.*

COMMENT

In this randomized, double-blind, placebo-controlled trial, selegiline had no significant effect on the course of sporadic ALS. Selegiline is a monoamine oxidase-B inhibitor with antioxidant properties.[12] After our study was completed, experimental evidence suggested that the loss of motor neurons in familial ALS is due to impaired regulation of free radicals formed by excessive oxidative processes.[2,13] In familial ALS, a mutation on chromosome 21 in the region encoding for the copper-zinc superoxide dismutase enzyme has been identified in 20% to 40% of patients.[2] Superoxide dismutase is 1 of 2 principal intracellular enzymes responsible for degrading intracellular free radicals.[2] In sporadic ALS, altered levels of glutathione reductase (another controller of antioxidants) has been identified, further implicating altered levels of antioxidants.[2] Results of animal experiments suggest that selegiline hydrochloride increases superoxide dismutase activity in the striatum of rats receiving 1 mg/kg per day for 3 weeks.[14,15] The dose given in this study, 10 mg/d, effectively inhibits 90% of monoamine oxidase-B within minutes of administration.[16]

The AALS rating scale is a clinically effective and reliable measure combining several different clinical scales to assess different areas affected in ALS using objective

and subjective information. The following 5 areas are tested: bulbar, respiratory, muscle strength, and arm and leg function. Recognizing that ALS affects individual patients in different areas of the body with variable severity, the AALS score assigns a weight to each region, giving the respective scores equal weight in the total score. Patients with pure bulbar disease can have a score showing a degree of clinical affliction similar to that seen in limb or respiratory involvement. Therefore, the total AALS score is an index of clinical severity, irrespective of the principal sites of involvement. The rate of symptom progression of 3.5 points per month was found in both centers, making reproducibility between centers high. Therefore, the scale is not only clinically useful but is also reproducible. Recent studies of a larger population of more than 800 patients confirmed the linearity of rate of progression.[7]

If oxidative abnormalities are important in the pathogenesis of ALS, there are several reasons why selegiline might not have been effective in our study. First, our entry criteria allowed patients with symptoms for as long as 3 years to enter. The disease might have been too far advanced to rescue the affected neurons. Second, the active agent, selegiline, may not have entered the central nervous system in sufficiently high quantities to affect spinal motor neurons. Third, the primary action may not be on the oxidative system, and the effect might be too weak to cause clinically evident change. Last, we failed to recruit the necessary 180 patients to reach a power of 80%, and a small clinical effect might have been detected if more patients had been recruited.

Accepted for publication May 21, 1997.

Supported by the Muscular Dystrophy Association of America, Tucson, Ariz.

Reprints: Dale J. Lange, MD, The Neurological Institute, Columbia-Presbyterian Medical Center, 710 W 168th St, New York, NY 10032.

REFERENCES

1. Lange DJ, Murphy PL, Maxfield RA, Skarvala A, Reidel G. Management of patients with amyotrophic lateral sclerosis. *J Neurol Rehab.* 1994;8:21-28.
2. Rosen DR, Siddique T, Patterson D, et al. Mutations in the Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. *Nature.* 1993;362:59-62.
3. Donaldson D, Fernando S, Murphy PL, et al. Blood superoxide dismutase, catalase, and glutathione peroxidase activity in amyotrophic lateral sclerosis. *Neurology.* 1995;45(suppl 4):221. Abstract.
4. Rothstein JD, Martin LJ, Kuncl RW. Decreased glutamate transport by the brain and spinal cord in amyotrophic lateral sclerosis. *N Engl J Med.* 1992;326:1464-1468.
5. Appel SH. A unifying hypothesis for the cause of amyotrophic lateral sclerosis, parkinsonism, and Alzheimer disease. *Ann Neurol.* 1981;10:499-505.
6. Westarp WE, Bartman P, Rossler J, et al. Antiretroviral therapy in sporadic adult amyotrophic lateral sclerosis. *Neuroreport.* 1993;4:815-822.
7. Smith RG, Hamilton HS, Holmann F, et al. Serum antibodies to L-type calcium channels in patients with amyotrophic lateral sclerosis. *N Engl J Med.* 1992;327:1721-1728.
8. The Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med.* 1989;321:1364-1371.
9. Younger DS, Rowland LP, Latov N, et al. Motor neuron disease and amyotrophic lateral sclerosis: relation of high CSF protein content to paraproteinemia and clinical syndromes. *Neurology.* 1990;40:595-599.
10. Appel V, Stewart SS, Smith G, Appel SH. A rating scale for amyotrophic lateral sclerosis: description and preliminary experience. *Ann Neurol.* 1987;22:328-333.
11. Appel SH, Stewart SS, Appel V, et al. A double-blind study of the effectiveness of cyclosporine in amyotrophic lateral sclerosis. *Arch Neurol.* 1988;45:381-386.
12. Cohen G, Spina MB. Deprenyl suppresses the oxidant stress associated with increased dopamine turnover. *Ann Neurol.* 1989;26:689-690.
13. Wiedau-Pazos M, Goto JJ, Rabizadeh S, et al. Altered reactivity of superoxide dismutase in familial amyotrophic lateral sclerosis. *Science.* 1996;171:515-517.
14. Knoll J. The pharmacology of selegiline (-) deprenyl): new aspects. *Acta Neurol Scand.* 1989; 126(suppl):83-91.
15. Carrillo MC, Kitani K, Kanai S, Sato Y, Miyatake K, Ivy GO. (-)Deprenyl increases activities of superoxide dismutase and catalase in certain brain regions in old male mice. *Life Sci.* 1994;54:975-981.
16. Heinonen EH, Myllyla V, Sotaniemi K, et al. Pharmacokinetics and metabolism of selegiline. *Acta Neurol Scand.* 1989;126:93-99.
17. Haverkamp LJ, Appel V, Appel SH. Natural history of amyotrophic lateral sclerosis in a database population: validation of a scoring system and a model for survival prediction. *Brain.* 1995;118:707-719.